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Fractionated stereotactic radiotherapy with Cyberknife® for primary spinal cord tumors

Treatment of spinal cord tumours with Cyberknife®

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Abstract

Aim: This study aimed to evaluate the efficacy and safety of Cyberknife® (Accuray, Sunnyvale, CA, USA) fractionated stereotactic radiotherapy (FSRT) in primary spinal cord tumors. The secondary aim is to present local control, post-treatment pain, neurological, and radiological response, and overall survival (OS) in the patients with spinal cord tumors.

Material and Methods: Fourteen patients with primary spinal cord tumors who underwent FSRT between July 2009 and October 2015 were retrospectively analyzed.

Results: The median dose delivered was 20 Gy (16-40), the median was 5 (3-6) fractions. The average follow-up period was 91 ± 40 months. After the treatment, in the evaluation of the first clinical response, it was determined that 5 (35.7%) patients had a decrease in symptoms, 6 (42.9%) patients were stable, 3 (21.4%) patients had no complaints. In the first radiological response evaluation, 2 (14.3%) patients had a complete response and 12 (85.7%) patients had a stable response. Vertebral compression fracture was detected as a late treatment side effect in one patient. According to the Kaplan-Meier analysis, the median five- and 10-year OS for patients with benign tumors was 115 months, 90% and 67.5 %, respectively; and the median five- and 10-year OS for the malign tumors patients was 76 months, 50 % and 25 %, respectively.

Discussion: FSRT appears to be a safe treatment modality, given the potential for late toxicity in patients with primary spinal cord tumors with high long-term survival rates, with few studies and limited follow-up time.

Keywords

Primary Spinal Cord Tumors; Cyberknife®; Fractionated Stereotactic Radiotherapy; Toxicity

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Introduction

Primary spinal cord tumors are rare tumors that represent only 3% of all central nervous system malignancies. It frequently located intradural or intramedullary, which distinguishes them from spinal cord metastases that are anatomically extradural [1].

Localization, cellular types, growth pace of spinal tumors and neurological status at presentation are essential parameters that determine the prognosis.

Complete surgical resection should be considered for most primary spinal tumors except for spinal lymphomas, if it is technically safe and available. Generally, only complete resection is curative for patients with low-grade histologies. Definitive radiotherapy is considered in medically inoperable patients, or definitive resection cannot be performed by preserving neurological function. Radiotherapy is indicated for tumors that are often incompletely resected, for those with nerve root transplantation, for high-grade tumors regardless of the resection size, and for most recurrent tumors [2].

In this case, standard fractionated external beam radiotherapy (EBRT) is used, but the adequate therapeutic radiation dose cannot be given due to dose limitations to spinal cord. Most primary tumors require high radiotherapy doses above the known spinal cord tolerance dose. To limit potential toxicities, guidelines recommend the bioequivalent dose (BED 2 Gy equivalent fractions) of 50 Gy [3]. In this case, it was reported that local failure rates due to EBRT may be relatively high [4].

The mechanism of fractionated stereotactic radiotherapy (FSRT) is specific for spinal cord tumors and is entirely different from the EBRT mechanism. It creates more double-strand breaks in DNA, repairs minor DNA damage, and even has anti-vascular effects, in situ vaccine effects, and abscopal effects [5,6]. Therefore, stereotactic radiotherapy provides effective local ablation therapy, and thus increases local control of the disease and overall survival (OS).

This study aimed to evaluate the efficacy and safety of Cyberknife® (Accuray, Sunnyvale, CA, USA) FSRT in spinal cord tumors. The secondary aim is to present local control and OS in patients with spinal cord tumors.

Material and Methods

Patients

This retrospective study was approved by the Medical Specialty Training Board of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (approval decision number: 08.10.15/1).

This retrospective study included 14 patients treated for primary spinal cord tumors who applied to the University of Health Sciences and the Dr Abdurrahman Yurtaslan Oncology Training and Research Hospital of Radiation Oncology between July 2009 and October 2015.

Treatment

According to the localization of the primary spinal cord tumor, patients wore a head-neck mask (Radon® Thermoplastic IMRT-A Head Shoulder Mask) and for planning purposes, immobilization devices with 4-dimensional Computed Tomography (4DCT) without contrast and 1.5 mm slice thickness CT were used.

Determination of the patients' target volume (TV) was achieved by fusing the images obtained by 3 mm slice thickness magnetic resonance imaging (MRI) scanning. The contrast-enhancing lesion on the MRI was delineated as gross tumor volume (GTV). The planned target volume (PTV) was created by giving a 1 mm margin around the GTV from all directions. T2-weighted magnetic resonance images delineate the spinal cord 6 mm above and 6 mm below the defined TV.

All patients were treated with the Cyberknife® device. The X-sight spine and 6D skull tracking technique were used. The plan of cyberknife ® FSRT isodose line of the patients is shown in Figure 1.

CT of bone structure, MRI of soft tissue and PET-CT for metabolic activity were used to evaluate the radiographic response using the Updated Response Evaluation Criteria in solid tumors (RECIST) [7]. The first follow-up imaging method was performed approximately three months after FSRT. Clinical response was assessed concurrently with imaging follow-up.

The 0-10 Numerical Rating Pain Scale (NRPS) was used to measure the pain response. In addition, various methods were used to assess neurological function, including the Medical Research Council (MRC) scale of 0-5 points for motor strength, the stinging test for numbness, the Romberg assessment for balance, and the test of the cranial nerves.

Statistical Analysis

All data were analyzed using the SPSS version 22 (IBM Corp., Armonk, New York, USA) statistical program. Descriptive statistics were calculated to determine the general characteristics of the groups. Frequency tables were used for ordinal variables, median and minimum/maximum values for non-normally distributed variables, mean ± standard deviation values for normally distributed variables. OS ratios were analyzed using the Kaplan – Meier method.

Results

The demographic and pathological features of the patients are shown in Table 1. A patient with recurrent (time of relapse after the first treatment was 62 months) medulloblastoma previously received RT to the craniospinal and posterior fossa. No surgery is considered in relapse, and FSRT is primarily applied in relapse. Chemotherapy was administered only to the case of recurrent medulloblastoma. Three patients with recurrent (relapse times after the first treatment are 48, 62 and 168 months, respectively) spinal ependymoma also received postoperative limited field-spinal RT in their initial treatments, and FSRT was performed as secondary irradiation.

After the treatment, when evaluating the first clinical response, it was determined that 5 (35.7%) patients had a decrease in symptoms, 6 (42.9%) patients were stable, 3 (21.4%) patients had no complaints. At the first radiological response evaluation, 2 (14.3%) patients had a complete response, and 12 (85.7%) patients had a stable response. Vertebral compression fracture was detected as a late treatment side effect in one patient.

During the median follow-up period of 91 ± 40 months (calculated from the time of each patient's first FSRT treatment), local recurrence occurred in 4 (28.6 %) patients.

According to the Kaplan-Meier analysis, the median, five- and 10-year OS for the benign tumors patients was 115 months (range: 25 -131 months), 90 % and 67.5 %, respectively, and the

median five- and 10-year OS for the malign tumors patients was 76 months (range: 12 -85 months), 50 % and 25 %, respectively. The properties of FSRT treatment and critical organ doses are showed in Table 2.

Table 1. Demographic characteristics and treatments of patients by primary spinal cancer

Variables	No of patients	%
Gender		
Male	7	50
Female	7	50
Age (years)		
Median (range, min-max)	45age	20-84 age
Pathological / radiological diagnosis		
Recurrent medullablastoma	1	7.1
Recurrent ependymoma	3	21.4
Schwannoma	2	14.3
Neurofibroma	1	7.1
Hemangioblastoma	1	7.1
Chordoma	2	14.3
Meningioma	4	28.6
Tumour histopathology		
Bening	10	71.4
Malignant	4	28.6
Surgery		
Subtotal resection	7	50
Gros total resection	4	28.6
Absent (radiological diagnosis)	3	21.4
Spine Levels Treated		
Cervical	7	50
Thoracic	4	28.6
Lumbar	2	14.3
Cervicothoracic	1	7.1
Indications for Stereotactic Radiosurgery		
Pain	8	57.1
Neurological Deficits	6	42.9
Asymptomatic/imaging progression only	-	-
Chemotherapy		
Yes	1	7.1
No	-	92.9

Table 2. Treatment features of FSRT

Parameter of Treatment	Mean (min-max)
Volume of PTV (mm^3)	4376.5 (644-10934)
Conformality index (CI)	1.8 (1.1-2.7)
Homogeneity index (HI)	1.2 (1-1.4)
Beam number (n)	148 (104-195)
Prescribed dose (cGy)	2000 (1600-4000)
Fraction number (n)	5 (3-6)
Isodose line (%)	83.1(70-93)
Max point dose PRV Renal Right (cGy)	1621 (538-2800)
Max point dose PRV Renal Left (cGy)	726 (83-1317)
Max point dose PRV spinal Cord (cGy)	2089 (417-2689)
Max point dose PRV Cauda equina (cGy)	1711 (99-2550)
Max point dose PRV Aorta (cGy)	1263 (583-1944)
Max point dose PRV esophagus (cGy)	380 (97-519)

PTV: planning target volume , PRV: planing organ-at-risk volume

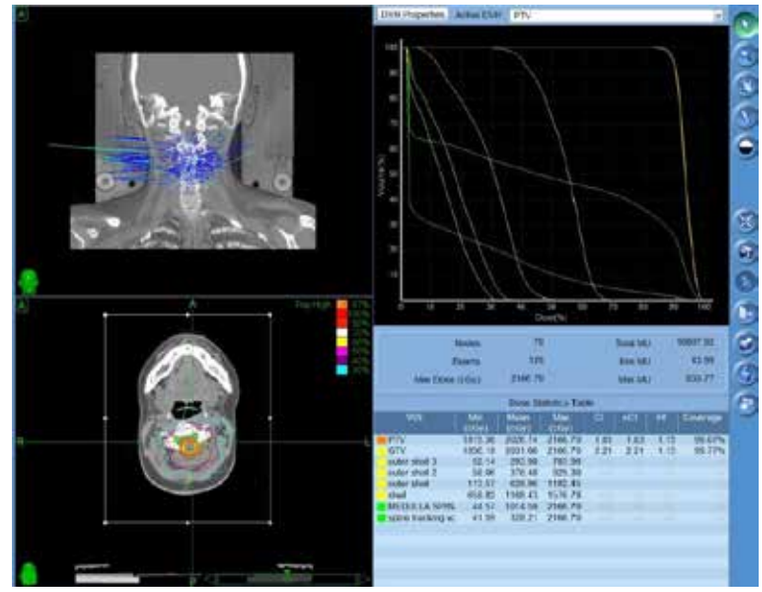

Figure 1. The plan of Cyberknife® FSRT and isodose lines of the patient with subtotal resection hemangioblastoma at the C5 vertebra level

Discussion

Due to the rarity of primary spinal cord tumors, there are few articles in the current literature on Stereotactic Radiosurgery (SRS) and FSRT for the treatment of these tumors. In our study, we aimed to evaluate the role of FSRT in the treatment of a limited number of patients with primary spinal cord tumors in our clinic.

Elibe et al., in their study on 30 patients with primary spinal cord tumors, reported SRS indication for pain in 19 (63.3%) patients, neurological deficit in 19 (63.3%), and asymptomatic only for radiological progression in 4 (13.3%) patients. Pain relief was observed in all patients presenting with pain during the follow-up of symptoms of patients who were given the median SRS dose of 16 Gy (10-24) (67% partial relief and 33% complete relief). In neurological deficit, it was reported that it was stable in 5 (31%) patients, and improvement was observed in 11 (69%) [8]. In a study conducted by Kufeld et al. with 39 patients with spinal meningioma and schwannoma, the median prescription dose of radiosurgery applied was 14 Gy. A decrease in pain level was reported in 8 of 19 patients with pain symptoms [9]. In our study, FSRT was indicated in 8 (57.1%) patients due to pain and 6 (42.9%) due to neurological deficit. These patients were monitored for symptoms. Partial symptom response was in 5 (35.7%) patients, stable response in 6 (42.9%) patients, and complete response in 3 (21.4%) patients.

Elibe et al., while providing local radiological control in 77% of the treated patients, they detected local-regional recurrence in 23% of them [8]. According to Kufeld et al., 19 lesions regressed in size, and 20 lesions were stable [9]. Chang et al. also reported their radiosurgery experience in 20 patients with 30 spinal cord lesions. Stereotactic radiotherapy/radiosurgery was applied in 1-5 fractions at doses of 14-33 Gy. While 57% of the lesions regressed, 33% were stable and 10% had progression [10]. Nineteen benign tumors were evaluated during a 25-month follow-up period after radiosurgery by Saghal et al. Tumor size was stable in 13 patients, regression in three patients, and

progression in three patients. The patients who progressed were diagnosed with two neurofibromas and one hemangioblastoma [11]. In our study, while local radiological control was achieved in 71.4% of cases, local regional recurrence was detected in 28.6% of cases.

Elibe et al. found long-term toxicity in two patients, which is thought to be associated with SRS. One of these patients had erector spine radionecrosis (patient received 16 Gy for S1 desmoid tumor), and the other had foot drop (patient received 10 Gy for L1-L2 glioma). Sixteen vertebral compression fractures were observed, none of which were associated with SRS [8]. In our study, a compression fracture was detected in a patient with long-term toxicity, which we think is associated with treatment (the patient received 40 Gy / 5 fraction therapy for L2 chordoma).

In our study, the median, five- and 10-year OS for the benign tumors patients was 115 months, 90% and 67.5%, respectively, and the median, five- and 10-year OS for the malign tumors patients was 76 months, 50 % and 25%, respectively. The limitation of our study is the small number of patients with different tumor histology. However, according to the publications in the literature, the follow-up period is a lengthy study.

Conclusion

FSRT appears to be a safe treatment modality, given the potential for late toxicity in patients with primary cord tumors with high long-term survival rates, with few studies and limited follow-up time. Studies with a higher number of patients and long-term follow-up are needed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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